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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/730,174	12/05/2000	Richard J. Zahradnik	IMUNE-001A	8045

7663 7590 10/01/2002

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/730,174	Applicant(s) ZAHRADNIK ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1-/9/02; 7/24/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-4,13,18,20,21 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-12,14-17,19,22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-24 are pending.

2. Applicant's election without traverse of Group VI, Claims 5-12, 14-17, 19, 22 and 24, drawn to a method for producing antibodies useful in the determination of PTH levels in a biological sample wherein said antibodies are capable of binding to a second peptide antigen having a formula of SEQ ID NOS: 3-6 and a kit comprising said antibodies.

3. Claims 1-4, 13, 18, 20-21 and 23 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 5-12, 14-17, 19, 22 and 24 are being acted upon in this Office Action.

5. The drawings, filed 12/5/00, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

6. The disclosure is objected to because of the following **informalities**: (1) SEQ ID is required on page 4, line 20, page 4, line 26, page 5, line 6 and line 12, and (2) Applicants should amend the Brief description of Drawings for Figures 1 and 2 to include SEQ ID NO. Appropriate action is required.

7 Claim 5 is objected to because (1) "same" in line 2 should have been "sample" and (2) it depends on non-elected SEQ ID NO: 1 and SEQ ID NO: 2.

8. Claim 15 is objected to because (1) claim 15 depends on itself and (2) "bovids" on line 2 should have been "bovines".

9. Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim(s) in

independent form. It is suggested that Applicants amend the preamble of claim 10 to recite a labeled antibody.

10. Claim 24 is objected to because claim 24 depends on non-elected claim 13.

11 The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 5-12, 14-16, 19, 22 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for producing antibodies useful on the determination of PTH levels in a biological sample comprising the steps: a) providing at least one first peptide antigen, wherein said at least one first peptide consisting of a peptide fragment of PTH selected from the group of SEQ ID NO: 3-6, a fragment consisting of amino acid residues 1-34 of human PTH, or a polypeptide comprising the full-length (1-84) PTH said full length (1-84) PTH being selected from the group consisting of species consisting of humans, rats, mice, bovines, dogs and pigs, b) administering *any* first peptide antigen to a host animal to induce antibody production against said at least first peptide antigen in said host animal; c) monitoring antibody titer produced by said administration of said at least one antigen to said host animal; d) isolating antisera produced in said host animal by said administration of said at least one peptide antigen; and e) selecting antisera from said isolated antisera produced in said host that is capable of binding to second peptide antigen, said second peptide antigen (4) "consisting of" a formula selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, (2) the antibody produced by the method mentioned above and (3) the test kits utilizing antibody produced by the method mentioned above for PTH detection assay, **does not** reasonably provide enablement for a method for producing *any* antibodies useful in the determination of PTH levels in a biological sample comprising the steps: a) providing at least one any first peptide antigen, said at least one (1) first peptide "comprising" any peptide fragment of PTH, (2) *any* first peptide antigen "comprises" amino acid residues 1-34 of PTH, or (3) *any* first peptide antigen "comprises" a formula selected from the group consisting of SEQ ID NO: 3-6, b) administering *any* first peptide antigen to a host animal such as mouse, rat and goat to induce antibody production against said at least first peptide antigen in said host animal; c) monitoring antibody

titer produced by said administration of said at least one antigen to said host animal; d) isolating antisera produced in said host animal by said administration of said at least one peptide antigen; and e) selecting antisera from said isolated antisera produced in said host that is capable of binding to second peptide antigen, said second peptide antigen (4) "having" or "comprising" a formula selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, (5) *any* antibody produced by the method mentioned above, and (6) *any* test kits utilizing *any* antibody produced by the method mentioned above for PTH detection assay. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of producing antibodies that bind specifically to SEQ ID NOS: 3-6 by immunizing a host with a peptide selected from the group consisting of SEQ ID NO: 3-6, a peptide consisting of amino acid residues 1-34 of human PTH, or a full length parathyroid hormone from humans, rats, mice, bovines, dogs and pigs as depicted in Figures 1 and 2 for PTH binding assays.

The specification does not teach how to make *any* antibody using the claimed method by administering *any* first peptide antigen wherein the first peptide antigen is *any* peptide fragment of PTH, (2) *any* first peptide antigen "comprises" amino acid residues 1-34 of PTH, or (3) *any* peptide antigen "comprises" a formula selected from the group consisting of SEQ ID NO: 3-6 that would bind specifically to a second peptide antigen comprising SEQ ID NO: 3-6 for any purpose. The term "comprising" is open-ended. It expands the "peptide fragment" to include additional amino acids at either or both ends. There is insufficient guidance as to what are the undisclosed amino acids to be added to any first or second peptide fragment of PTH. Further, there are no working example in the specification demonstrating that immunizing a host with *any* fragment of PTH would generate antibody that binds **specifically** to a second peptide antigen

such as SEQ ID NO: 3-6 (that are fragments of PTH) or a second peptide antigen "comprising" a formula from the group consisting of SEQ ID NO: 3-6, which read on the full-length PTH since the term "comprising" is open-ended. Again, it expands the second peptide antigen to include additional amino acid at either or both ends. The specification discloses that SEQ IDD NOS: 3-6 are fragments of PTH.

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed amino acids that can be added, it is unpredictable which undisclosed peptide fragment would be useful for any purpose, especially for PTH assay measurements that minimize cross-reactivity with the large 1-84 PTH fragment.

Colman *et al* teach that even a single amino acid changes within the interface of an antibody-antigen can raise or lower the affinity of the antibody (See page 33, in particular).

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the indefinite number of undisclosed amino acid sequence to be added to the first or second peptide fragment (without the specific structure such as the specific amino acid residues), it is unpredictable that immunizing with an undisclosed amino acid sequence and peptide fragment will have the same antibody specificity as the antibody that binds specifically to SEQ ID NO: 4-6, in turn, would be useful for any purpose. Since the peptide fragment is unknown, it is unpredictable which undisclosed peptide fragment would be useful for a method for producing antibodies that would bind specifically to the SEQ ID NO: 4-6. Since the method of producing antibodies that would bind specifically to the SEQ ID NO: 4-6 is not enabled, it follows that the antibody produced by said method is not enabled. It also follows that the conjugate of said antibody and the test kits utilizing said antibody are not enabled. With regard to the first peptide fragment "comprising" the (1-34) PTH peptide fragment, the term "comprising" is open-ended. It expands the (1-34) PTH peptide fragment to include additional amino acid at either or both ends. There is insufficient guidance and working example as to what type of amino acid could be added, in turn, the antibody produced by immunizing said undisclosed peptide fragment would bind specifically to PTH. Since the (1-34) PTH peptide fragment selected from a group of species consisting of humans, rats, mice, bovines, dogs, and

pigs is not enabled, it follows that said (1-34) PTH peptide fragment has a carrier protein coupled therewith is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

13. Claims 5-12, 14-16, 19, 22 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method for producing *any* antibodies useful in the determination of PTH levels in a biological sample comprising the steps: a) providing at least one any first peptide antigen, said at least one (1) first peptide "comprising" any peptide fragment of PTH, (2) *any* first peptide antigen "comprises" amino acid residues 1-34 of PTH, or (3) *any* first peptide antigen "comprises" a formula selected from the group consisting of SEQ ID NO: 3-6; b) administering *any* first peptide antigen to a host animal such as mouse, rat and goat to induce antibody production against said at least first peptide antigen in said host animal; c) monitoring antibody titer produced by said administration of said at least one antigen to said host animal; d) isolating antisera produced in said host animal by said administration of said at least one peptide antigen; and e) selecting antisera from said isolated antisera produced in said host that is capable of binding to second peptide antigen, said second peptide antigen (4) "having" or "comprising" a formula selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, (5) *any* antibody produced by the method mentioned above, and (6) *any* test kits utilizing *any* antibody produced by the method mentioned above for PTH detection assay.

The specification discloses only a method of producing antibodies that bind specifically to SEQ ID NOS: 3-6 by immunizing a host with a peptide selected from the group consisting of

SEQ ID NO: 3-6, a peptide consisting of amino acid residues 1-34 of human PTH, or a full length parathyroid hormone from humans, rats, mice, bovines, dogs and pigs as depicted in Figures 1 and 2 for PTH binding assays.

With the exception of the specific first and second peptide antigens mentioned for a method of producing antibodies useful in the determination of PTH levels in a biological sample, there is insufficient written description about the structure associated with function of (1) *any* first peptide "comprising" *any* peptide fragment of PTH, (2) *any* first peptide antigen "comprises" amino acid residues 1-34 of PTH, or (3) *any* first peptide antigen "comprises" a formula selected from the group consisting of SEQ ID NO: 3-6, (4) *any* second peptide antigen "having" or "comprising" a formula selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, (5) *any* antibody produced by the method mentioned above, and (6) *any* test kits utilizing *any* antibody produced by the method mentioned above for PTH detection assay. The term "comprising" or "having" is open-ended. It expands the peptide fragment to include additional amino acid residues at either or both ends. Further, given the lack of a written description of *any* additional representative species of first peptide fragment of PTH, and second peptide fragment, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 5-7, 9, 11-12, 14, 15, 16, 19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Ratcliffe *et al* (J Immunol Methods 127(1):109-16, Feb 1990; PTO 892).

Ratcliffe *et al* teach a method for producing antibodies such as 17 monoclonal antibodies to human parathyroid hormone-related protein (PTH-rP) 1-34 useful in the determination of PTH levels. The reference method comprises the steps of administering at least a first peptide antigen such as PTH-rP peptide fragment 1-18, 9-23, 1-34, 18-34, and 22-34 of human PTH (See Fig 1, page 110, column 2, in particular) to a host animal such as mice to induce antibody production against the reference first peptide in said host animal, monitoring antibody titer produced by said host animal and isolating antisera produced by said host (See abstract, Materials and Methods, in particular). Four of the reference antibodies such as 1F3, 1D5, 4E9 and 4F9 are shown to be of high avidity to PTH-rP 1-34 (See abstract, in particular), which is a second peptide antigen "comprises" or "having" a formula of the claimed SEQ ID NO: 3 (See Fig 1, Table III, in particular). The reference peptide fragment has a carrier protein such as BTG coupled therewith (see page 111, column 1, Table 1, Materials and Methods, Preparation of Conjugate, in particular). The term "comprising" or "having" is open-ended. It expands the claimed peptide fragment to include the additional amino acid residues at either or both ends to read on the reference peptide fragment. Thus, the reference teachings anticipate the claimed invention.

16. Claims 5-7, 9, 11-12, 19, 22 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 4,341,755 (July 1982, PTO 892).

The '755 patent teaches a method for producing antibodies useful in the in the determination of PTH levels comprising the steps of administering at least a first peptide antigen such as human PTH 65-84 to a host animal such as chicken to induce antibody production against the reference first peptide in said host animal, monitoring antibody titer produced by said host animal and isolating antisera produced by said host (See entire document, column 7, lines 19-23, in particular). The reference antibody is capable of binding to a second peptide antigen such as intact human PTH which comprising the claimed formula of SEQ ID NO: 3 (See column 7, line 22, in particular), or intact bovine PTH having or comprising the claimed formula of SEQ ID NO: 6 (See column 7, line 33, in particular) or rat PTH comprising the claimed formula of SEQ ID NO: 5 (See column 7, line 39, in particular). The '755 patent teaches the antibodies can be raised in rabbits and other animals (See column 8, lines 65-66, in particular). The reference peptide antigen is labeled such as I-125, in particular (See column 9, lines 47-53, in particular). The '755

patent further teaches the reference antibodies are useful in a kits for determining bioactive intact PTH (See column 8, line 61-63, Claims of '755, in particular). Thus, the reference teachings anticipate the claimed invention.

17. Claims 5-7, 9, 11-12, 14-17, 19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Ikeda *et al* (J Clin Endo & Metabolism 79(6): 1322-27, 1994, PTO 892)

Ikeda *et al* a method of for producing antibodies useful in the in the determination of PTH levels comprising the steps of administering at least a first peptide antigen such as human PTH 1-34 and PTH (1-84) to a host animal such as mice and rabbit to induce antibody production against the reference first peptides in said host animal, monitoring antibody titer produced by said host animal and isolating antisera produced by said host (See page 1323, Materials and Methods, in particular). Ikeda *et al* further teach the reference peptide antigens are conjugated to carrier protein such as thyroglobulin (See page 1323, column 1, Preparation of Antibodies, in particular). The reference antibodies bind specifically to a second peptide antigen such as the full length human PTH (See page 1326, column 1, Discussion, in particular). Claims 6, 12 and 19 are included in this rejection because the term "comprising" is open-ended. It expands the claimed sequence of SEQ ID NO: 3 to read on the intact PTH (1-84) that inherently has the amino acid residues 1-34 of PTH. Thus, the reference teachings anticipate the claimed invention.

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 5 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ratcliffe *et al* (J Immunol Methods 127(1): 109-16, Feb 1990; PTO 892) or US Pat No. 4,341,755 (July 1982, PTO 892) or Ikeda *et al* (J Clin Endo & Metabolism 79(6): 1322-27, 1994; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 92-94, pages 323-358).

The teachings of Ratcliffe *et al*, the '755 patent, and Ikeda *et al* have been discussed supra.

The claimed invention in claim 8 differs from the reference only by the recitation that the method wherein the host animal is goat.

The claimed invention in claim 10 differs from the reference only by the recitation that the antibody further includes a label covalently attached thereto said label being selected from the group consisting of radioactive, fluorescent, enzymatic and dye tracers.

Harlow *et al* teach a method of producing polyclonal and monoclonal antibody and the choice of animal for immunization is determined by (1) the amount of serum desired, (2) the evolutionary distance between the species from which the antigen is isolated, and (3) how much antigen is available (See page 93, in particular). Harlow *et al* teach immunizing host animal such as sheep (goat) give large volumes of sera (See page 93, in particular) and the antigens such as PTH derived from human, mice, rat, bovine and dog are evolutionary distant from sheep (See page 93, in particular). Harlow *et al* further teach a method of labeling any antibody such as radioactive iodine, enzyme such as peroxidase, alkaline phosphatase, fluorochrome such as flourescein, rhodamine, Texas red and dye tracer (See page 323-358, in particular). The advantages of radiolabeling antibody are easy to quantitate, easy to label directly and with high sensitivity while the advantages of enzyme or fluorochromes labeled antibody are long shelf life, and high sensitivity (See page 322, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce polyclonal antibody by immunizing a goat as taught by Harlow *et al* with the PTH-rP peptide fragment 1-18, 9-23, 1-34, 18-34, and 22-34 of human PTH as taught by Ratcliffe *et al*, the human PTH 65-84 peptide antigen as taught by the '755 patent, or the human PTH 1-34 and PTH (1-84) first peptide as taught by Ikeda *et al* and covalently attached a label such as radioisotope, fluorescent, enzymatic and dye tracers to the antibody as taught by Harlow *et al*. From the combined teachings of the references, it is apparent that one of

ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach immunizing host animal such as sheep (goat) give large volumes of sera (See page 93, in particular) and the antigens such as PTH derived from human, mice, rat, bovine and dog are evolutionary distant from sheep (See page 93, in particular). Harlow *et al* further teach the advantages of radiolabeling antibody are easy to quantitate, easy to label directly and with high sensitivity while the advantages of enzyme or fluorochromes labeled antibody are long shelf life, and high sensitivity (See page 322, in particular). The labeled antibodies are useful for determining PTH levels in biological sample as taught by Ratcliffe *et al*, the '755 patent, and Ikeda *et al*.

21. Claims 5-6, 12 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ratcliffe *et al* (J Immunol Methods 127(1):109-16, Feb 1990; PTO 892) or Ikeda *et al* (J Clin Endo & Metabolism 79(6): 1322-27, 1994; PTO 892) in view of US Pat No. 4,341,755 (July 1982, PTO 892) or U.S. Pat No. 6,107,049 (filed Dec 8, 1997, PTO 892; see entire document).

The teachings of Ratcliffe *et al* and Ikeda *et al* have been discussed supra.

The claimed invention in claim 24 differs from the references only by the recitation that the test kits and analytical procedures used for the determination of bioactive intact PTH utilizing the antibody produced by a method for producing *any* antibodies useful in the determination of PTH levels in a biological sample comprising the steps: a) providing at least one any first peptide antigen, said at least one first peptide "comprising" any peptide fragment of PTH; b) administering *any* first peptide antigen to a host animal such as mouse, rat and goat to induce antibody production against said at least first peptide antigen in said host animal; c) monitoring antibody titer produced by said administration of said at least one antigen to said host animal; d) isolating antisera produced in said host animal by said administration of said at least one peptide antigen; and e) selecting antisera from said isolated antisera produced in said host that is capable of binding to second peptide antigen, said (4) second peptide antigen "comprises" a formula selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6.

The '755 patent teaches a method for producing antibodies useful in the in the determination of PTH levels comprising the steps of administering at least a first peptide antigen

such as human PTH 65-84 to a host animal such as chicken to induce antibody production against the reference first peptide in said host animal, monitoring antibody titer produced by said host animal and isolating antisera produced by said host (See entire document, column 7, lines 19-23, in particular). The '755 patent further teaches the reference antibodies are useful in a kits for determining bioactive intact PTH (See column 8, line 61-63, Claims of '755, in particular).

The '049 patent teaches a kit comprising an antibody specific for cPSA for diagnostic assays, separation and detection assays (See column 11, line 44-57, claims 12-17 of '049, in particular). The '049 patent teaches the reference antibody is immobilized on a solid carrier such as a plate, magnetic particle which are beads wherein the antibody is fluorescein labeled or enzymatically labeled such as alkaline phosphatase (See column 11, lines 46-49, claims 18-20 of '049, in particular). The '049 patent further teaches the method of detection is conveniently provided in the form of a kit that is a packaged collection of reagents or combination of other assay components as necessary and appropriate for the needs of the user (See column 9, lines 46-51, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to put the antibody taught by Ratcliffe *et al* or Ikeda *et al* in a kit as taught by the '755 patent or the '049 patent for the determination of bioactive intact PTH utilizing the antibodies as taught by Ratcliffe *et al*, and Ikeda *et al*. One would have been motivated, with a reasonable expectation of success, to place the antibody in a kit as taught by the '049 and the '755 patent for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '049 (See column 9, lines 46-51, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references.

22. Claims 5, 15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ratcliffe *et al* (J Immunol Methods 127(1):109-16, Feb 1990; PTO 892), U.S Pat No. 4,341,755 (July 1982, PTO 892) or Ikeda *et al* (J Clin Endo & Metabolism 79(6): 1322-27, PTO 892) each in view of Heinrich *et al* (J Biol Chem 259(5): 3320-3329, March 1984; PTO 892).

The teachings of Ratcliffe *et al*, the '755 patent and Ikeda *et al* have been discussed supra.

The claimed invention in claim 17 differs from the references only by the recitation that the at least one first peptide antigen comprises intact, full-length (1-84) from species of humans, rats, bovines, and pigs.

Heinrich *et al* teach the amino acid sequence of rat parathyroid hormone is highly conserved near the N-terminus among the various species such as bovine, humans, pigs (porcine) (See Abstract, Fig 9, in particular) and this conservation in the NH2 terminus of PTH (+1 to +15) region is consistent with the analyses of synthetic fragments and analogs of PTH that have shown for full biological activity (See page 3328, column 1, second full paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the first peptide antigen as taught by Ratcliffe *et al*, the '755 patent or Ikeda *et al* for the intact full length PTH from humans, bovine, rats, or porcine as taught by Heinrich *et al* for a method for producing antibodies useful in the determination of PTH levels in a biological sample as taught by Ratcliffe *et al*, the '755 patent and Ikeda *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Heinrich *et al* teach the amino acid sequence of rat parathyroid hormone is highly conserved near the N-terminus among the various species such as bovine, humans, pigs (porcine) (See Abstract, Fig 9, in particular) and this conservation in the NH2 terminus of PTH (+1 to +15) region is consistent with the analyses of synthetic fragments and analogs of PTH that have shown for full biological activity (See page 3328, column 1, second full paragraph, in particular).

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any

inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

25. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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